claimed methods can include all organic compounds. The Office Action further asserts that the specification does not provide adequate guidance as to how to generically perform the sib selection process because the desired product would be in a vanishingly small population and any signal would likely be drowned out by the vast majority of background signals from exogenous products so that the procedure is practically limited to desired molecules with huge signals which are easy to detect. The Office Action additionally asserts that even if the signal were detectable, sib selection requires one to select one sib that contains the desired activity and produce more of this half of the population, which would be possible only in a single type of population, and the specification lacks guidance to perform this type of selection on libraries other than gene products cloned into bacteria. Finally, the Office Action asserts that characterization of the desired product would require unique identification, which would involve extensive assays to isolate a set of characteristics within a complex mixture and that one would have no way to determine which of the components of the mix is providing which set of characteristic properties. Applicant respectfully traverses this rejection.

In contrast to the assertions in the Office Action, it is respectfully submitted that the specification provides enablement in compliance with 35 U.S.C. 112 for the claimed methods of generating new compounds using random chemical reactions to produce a diversity of unknown compounds which are screened for one or more desired properties to detect the presence of suitable compounds. Applicants agree that these

methods may employ essentially all chemical compounds and as such, the scope of the number of compounds applicable in the methods is generic. However, the scope of the claims is only one factor to be considered in determining the adequacy of the enablement provided by the specification for the claimed invention.

The test of enablement is whether one reasonably skilled in the art could practice the invention from the disclosures in the patent application coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

A proper undue experimentation analysis should be made considering the factors enumerated in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) to determine whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Although the scope of the pending claims is broad, the state of the art of chemical and enzymatic synthesis and screening assays is highly developed as is apparent from the references of record. Further, the level of skill in these arts is high, as is the probability of finding desired compounds according to the invention as particularly disclosed in the specification. Moreover, the inventor has provided extensive direction for practicing the claimed methods, including working examples. The specification provides all necessary details regarding the chemical reactions that provide for a highly diverse library of products from a starting group of organic molecules and the methods of identifying desired molecules in the product libraries.

First, the specification teaches the starting group of organic molecules to use. More specifically, the specification teaches that the starting compounds can include all organic compounds, including, for example, alkanes, alkenes, alkynes, alcohols, ethers, amines, aldehydes, ketones, acids, esters, amides, cyclic compounds, heterocyclic compounds, hetero-atom bearing compounds, amino acids and nucleotides (page 9, lines 19-24).

Second, the specification teaches the reactants that can be used to perform a series of diverse chemical reactions on the starting molecules. For example, the specification teaches

that diverse chemical reactions can be catalyzed by exogenously added polypeptide enzymes, or other sets of candidate enzymes such as antibody libraries, protein libraries, nucleic acid molecule libraries, and libraries of core building blocks and adducts (page 20, line 9, to page 21, line 22). Where the chemical reactions are catalyzed by protein-based enzymes, the enzymes can include, for example, oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases (page 22, line 23, to page 23, line 12). Additionally, the specification teaches that diverse chemical reactions can be catalyzed by the population of substrates themselves (page 18, line 29, to page 19, line 4).

Alternatively, the specification teaches that the chemical reactions need not be catalyzed by enzymes. To perform the methods with respect to non-enzymatic reactions, the substrates can be reacted, for example, with dehydrating agents, reducing agents, oxidizing agents, heat or light. The specification provides examples of such agents and their uses (page 35, line 3, to page 37, line 24).

Third, the specification teaches the conditions under which the chemical reactions can be performed. For example, the specification provides guidance regarding reaction volumes, reactant concentrations and solubility considerations (page 23, line 13, to page 24, line 25); reaction times and temperatures (page 25, lines 14-16); and appropriate cofactors to add(page 25, lines 16-20) for performing the claimed methods with enzymes. The specification also provides guidance as to methods for separating catalysts from substrates, which can be useful for

performing the enzymatic reactions sequentially (page 24, line 26, to page 25, line 14).

With respect to non-enzymatic methods for performing chemical reactions, the specification teaches appropriate conditions, such as solvents, reaction times, temperatures and pressures, for use with dehydrating agents, reducing agents, oxidizing agents, heat or light (page 35, line 3, to page 37, line 24).

By following the methods taught in the specification, the skilled artisan would arrive at a mixture containing a high diversity of organic molecules. Therefore, it is respectfully submitted that the specification adequately enables the generation of a high diversity of organic molecules according to the claimed methods.

Further, the Examiner's attention is directed to the extensive guidance in the specification for characterizing products without undue experimentation. The specification provides the necessary guidance to screen for and, if desired, to isolate, a molecule having a desired property from the diversity of products generated by the methods described above.

With respect to the multiple screening methods disclosed, the specification teaches that exemplary molecules of interest include molecules with the properties of acting as drugs, vaccines, liganding agents, catalysts, catalytic cofactors, structures of use, detector molecules and building

blocks for other compounds (page 8, line 26, to page 9, line 18). The skilled person understands that the particular screening method will necessarily depend on the property of interest; however, given the guidance in the specification, and the extensive knowledge in the art regarding methods of screening for pharmaceutically and industrially useful compounds, the skilled person could have adapted such methods to any property of interest, without undue experimentation.

With respect to the examiner's comments regarding the operability of the sib selection method, the specification teaches exemplary methods to identify low concentrations of receptor ligands from a mixture of molecules, by identifying the activation of cellular signaling pathways by the ligand (page 37, line 25, to page 38, line 30). Likewise, low concentrations of ligands can be identified by a variety of direct and competitive binding assays known in the art (page 39, line 10, to page 41, line 31). Receptor ligands can act by antagonizing, agonizing, substituting for, or modifying the effects of the natural hormone, and are thus candidate drugs for treatment of a variety of conditions (page 38, lines 12-16).

Additionally, the specification teaches an exemplary method of detecting a molecule with the property of inhibiting an enzymatic reaction, by screening the product mixture for inhibition of the enzymatic reaction of interest (page 42, lines 1-10). Similarly, the specification teaches that a molecule that is a catalyst, or cofactor, of a particular enzymatic reaction can be detected by determining the ability of the product mixture

to cause an increase in production of the product of the catalyzed reaction (page 43, lines 5-8). Methods are well known in the art to prepare and detect chromogenic or fluorogenic reactants or products of an enzymatic reaction of interest, as well as to use antibody binding or shape complement techniques to identify such molecules (page 43, lines 12-21).

From a product mixture containing a molecule having a property of interest, the specification teaches methods for characterizing and/or isolating the molecule. For example, in order to determine the structure of the molecule of interest, the product mixture can be contacted with a solid support containing moieties that bind the molecule, such as a receptor or antibody. The molecules that are retained on the support can subsequently be freed in an isolated form. The structure of the molecule can then be determined by analytical means, such as mass spectroscopy and the like (page 43, line 27, to page 44, line 15).

Alternatively, the specification teaches that the product mixture can be winnowed to progressively smaller subsets, containing a higher concentration of the desired product, by reducing the set of initial substrates, or set of chemical reactions. The structural or functional properties of the product within the winnowed mixture can then be characterized and the product isolated (page 44, line 16, to page 47, line 21) using the multiple methods discussed above for detecting low concentrations of molecules in a mixture.

The Office Action fails to support the rejection with specific scientific reasons why these disclosed sensitive and specific screening assays would not be operable when used "to generically perform applicant's sib selection process" or "to isolate a set of characteristics within a complex mixture" or "to determine which of the components of the mix is providing which set of characteristic properties". Considering the developed state of the art of screening for desired molecules at subnanomolar and subpicomolar concentrations, and the high level of skill in the art, only routine experimentation would be required to practice the methods according to this invention.

Therefore, it is respectfully submitted that the specification enables the claimed methods of production of an organic molecule having a desired property.

In view of the above remarks, it is respectfully submitted that the specification adequately enables the methods of claims 1-50. Accordingly, withdrawal of the rejection under 35 U.S.C.
§ 112, first paragraph, is respectfully requested.

Rejection under 35 U.S.C. § 103

Claims 1-50 stand also rejected under 35 U.S.C. § 103(a) as allegedly obvious over Jacobs et al., Trends Biochem., 12(1):19-26, 1/1994 for the reasons of record. Applicant has pointed out that the Jacobs et al. publication is a post priority date reference and as such does not constitute valid prior art.

The Office Action asserts that art cited within the Jacobs et al. review article is relevant and relies on Jacobs' statements of the earlier publications as the basis for the rejection. However, publications which are the basis of rejections under 35 U.S.C. § 102 and 35 U.S.C. § 103(a) must antedate the effective date of a patent application. Accordingly, the rejection of claims 1-50 over Jacobs et al. is improper and should be withdrawn.

35 U.S.C. § 102 states that "A person shall be entitled to a patent unless - (a) the invention was described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent." The date printed on the publication is considered *prima facie* to be the critical date of the reference as prior art received by members of the public. Although some references which do not have prior art dates have been accepted by the courts as a showing of the state of the art for purposes of overcoming a rejection under 35 U.S.C. § 112, first paragraph or the level of ordinary skill in the art, non prior art references may not be used in a rejection under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) to teach the limitation of the claims *per se*. See In re Glaberson, 253 F.2d 430, 45 C.C.P.A. 854, 117 U.S.P.Q. 217 (C.C.P.A. 1958)in which Judge Giles Rich reversed an appealed prior art rejection based on the examiner's legal error in using a reference subsequent to the filing date of the rejected claims as the basis of the prior art rejection.

The Office Action appears to be relying on the teachings of some of the specific references cited in the Jacobs et al. review article. Where a reference is relied on to support

a rejection, whether or not in a minor capacity, that reference should be positively included in the statement of the rejection. See *In re Hoch*, 428 F.2d 1341, 1342 n.3 166 USPQ 406, 407 n. 3 (CCPA 1970). It is important for an examiner to properly communicate the basis for a rejection so that the issues can be identified early and the applicant can be given fair opportunity to reply. That has not been done in this instance.

The Office Action states that "what is relevant is the publication date of the prior art which Jacobs reviews." However, 37 C.F.R. § 104 requires that when rejecting claims for want of novelty or for obviousness, the examiner must cite the best references at his or her command. If in fact "what is relevant is the publication date of the prior art which Jacob reviews" as the Office Action argues, then it follows that the best references would be specific references cited by the review articles, both because they may have publication dates prior to effective filing date of this application and because such references may have the specific teachings on which the Examiner plans to rely.

Given that Jacobs et al. is a post-priority publication, it is respectfully submitted that the Office Action has not supported the allegation that the teachings referred to in Jacobs et al. are actually found in the prior art. Further, the Office Action has failed to point out which of the many references cited by Jacobs et al. would form the basis of any such rejection. It follows that the Office Action has also not set forth where in the prior art the relevant teachings are found. No copies of any relevant prior art references have been

provided to the Applicant so they may be considered for everything they teach. Nor has the Office Action indicated what are considered to be the differences between claims 1-50 and the primary references, and proposed modifications over the prior art necessary to arrive at the claimed subject matter, and has not provided an explanation of the motivation for one skilled in the art, at the time the invention was made, to make the proposed modification.

The Office Action further states that "applicant has not distinguished the claims from the prior art taught in Jacobs and therefore presumably applicant is conceding that the claims read on the features pointed out in Jacobs." This conclusion is legally erroneous because that the burden of going forward with a response is not shifted to the Applicant until the Examiner has established a proper *prima facie* rejection. In this application, the examiner has failed to establish a *prima facie* case of obviousness of claims 1-50 over the teachings of the Jacobs et al. review article for the reasons given above. Accordingly, the burden has not been shifted to the Applicant to distinguish the claims from those references. In the absence of specifically set forth grounds for rejection under 35 U.S.C. § 103 in the Office Actions, Applicants are unable to address the assertion that it would have been *prima facie* obvious to arrive at the claimed invention.

Applicants respectfully request the Examiner to either withdraw Finality of the Office Action and clarify any grounds for rejection under 35 U.S.C. § 103 with reference to teachings found in the prior art, or, if no new rejection applies, to

withdraw the rejection under 35 U.S.C. § 103 and indicate that the claims are free of the prior art.

CONCLUSION

In light of the Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call Cathryn Campbell or the undersigned attorney.

Respectfully submitted,

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